A COMPREHENSIVE ANALYSIS OF DNA METHYLATION IN HEAD AND NECK SQUAMOUS CELL CARCINOMA INDICATES DIFFERENCES BETWEEN VIRAL AND CHEMICAL INDUCED CARCINOGENESIS

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Background: Head and neck squamous cell carcinomas (HNSCC) are the eighth most commonly diagnosed cancers in the U.S population. The risk of developing HNSCC is increased with exposure to tobacco, alcohol and infection with human papilloma virus (HPV). HPV-induced cancers have a distinct risk profile as well as improved prognosis compared to chemically induced cancers associated with tobacco exposure and alcohol use. Epigenetic changes are an important mechanism in carcinogenic progression, but how these changes differ between viral- and chemical-induced head and neck cancers remains unknown.

Methods: We quantified CpG methylation at 1505 CpG sites across 807 genes in 70 well-annotated HNSCC tumor samples from the University of Michigan Head and Neck SPORE patient population using the Illumina Goldengate Methylation Cancer Panel. CpG methylation levels at each locus were normalized based on probe length and guanine-cytosine content.

Results: Unsupervised hierarchical clustering based on methylation values identified 3 distinct tumor clusters, which were found to significantly differ by age and smoking status. HPV status did not differ between clusters, indicating some common shared epigenetically-regulated pathways between chemically- and HPV-induced tumors. Weighted linear modeling was used to identify differentially methylated genes based on epidemiological characteristics. Consistent with previous *in vitro* findings by our group, methylation of sites in the *CCNA1* promoter region was found to be significantly higher in HPV+ tumors. After adjusting for cancer site, stage, age, gender, alcohol consumption, and smoking status, HPV status was found to be a statistically significant predictor for DNA methylation at an additional 11 genes, including *CASP8* and *SYBL1*.

Conclusions: Findings from this study provide insight into the epigenetic regulation of viral vs. chemical carcinogenesis and could provide novel targets for development of individualized therapeutic regimens based on environmental exposures.

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